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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,050	05/17/2001	Hidetoshi Uemura	UEMURA 8	4088

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/856,050	UEMURA ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 20 July 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *amendment to claim 1 would require a new 112, second paragraph rejection -see attached.*

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached.*

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none.*

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-6,12-18,20,25,27,30.*

   Claim(s) withdrawn from consideration: *19,21-24,26,28 and 29.*

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *PTO 892*

ADVISORY ACTION

1. Claims 1-6 and 12-30 are pending.

2. The period for reply continues to run from the date of the final rejection. Any extension of time must be obtained by filing a petition under 37 CRF 1.136(a) accompanied by the appropriate fee. The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. A reply within the meaning of 37 CFR 1.113 must be timely filed to avoid abandonment of this application.

3. The request for entering amendments to claims 1-6, 20, 27, cancellation of claims 19, 21-24, 26, 28-29 and arguments filed on 7/20/2004 under 37 CFR 1.116 in reply to the Final Action Paper mailed on 4/21/2004 are acknowledged. While the proposed amendments to claims 1-6, 20, 27 appear to overcome some of the objections and grounds of rejections previously applied under 35 USC 112, second paragraph, the claims as amended introduce new grounds of rejections under 35 USC 112 second paragraph and do not overcome a claim objection previously applied as discussed below. If the claims were to be amended as suggested below, objections and rejections under 35 USC 112, second paragraph may be overcome. However, these amendments would not be sufficient to overcome the 35 USC 103(a) rejection previously applied to claims 1-4, 12, 14-16, 18, 20, 25, 27 and 30 for the reasons of record and those further discussed below.

4. Proposed amended claim 1 and claims 2-6, 12-18, 20, 25, 27, 30 dependent thereon would be rejected under 35 USC 112, second paragraph due to the recitation of "(c) a nucleotide sequence encoding a polypeptide comprising.....wherein said polynucleotide is cleavable by an enterokinase.." for the following reasons. First, there is no antecedent basis for the "polynucleotide cleavable by an enterokinase". Second, it is unclear as to how an enterokinase, which cleaves proteins, can cleave a polynucleotide. The term should be replaced with "(c) a

nucleotide sequence encoding a polypeptide comprising...wherein said polypeptide is cleavable by an enterokinase".

5. Proposed amended claim 6 would be objected to due to the recitation of "wherein the polynucleotide encoding at least one amino acid residue comprises at least a nucleotide sequence encoding amino acids 36-40 of SEQ ID NO: 19..". While Applicants have partially amended the claim as suggested, the term "wherein the polynucleotide encoding at least one amino acid residue comprises at least a nucleotide sequence encoding...." should be amended to recite "wherein the polynucleotide encoding at least one amino acid residue comprises a nucleotide sequence encoding at least amino acid residues 36-40....". See page 2, paragraph 1 of the Final Action.

6. Claim 13 would be rejected under 35 USC 112, second paragraph in view of proposed amended claim 2 as it lacks antecedent basis for the term "wherein the nucleotide sequence encoding the target protein is that encoding neurosin" As indicated in the Final Action, pages 3-4, paragraph 7, last sentence, some claims dependent upon claim 2 may need to be amended according to the changes made to claim 2 to maintain proper antecedent basis. In proposed amended claims 2, the term "nucleotide sequence encoding the target protein" is no longer part of item (d). Claim 13 would have to be amended to recite "wherein the polynucleotide encoding the target protein is that encoding neurosin".

7. As indicated in the Final Action, page 8, paragraph 16, Applicants are advised that should claims 18 and 20 be found allowable, claims 25 and 27 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Since claim 14 is directed to a host cell transformed

with the vector of claim 2, claims 25 and 27 both require cultivating the same host cell as that of claims 18 and 20, respectively.

8. Even if proposed amended claims 1-6, 20, 27 were entered, claims 1-4, 12, 14-16, 18, 20, 25, 27, and 30 would remain rejected under 35 U.S.C. 103(a) as being unpatentable over the Invitrogen 1998 product catalog. As indicated in the Final Action, the Invitrogen 1997 catalog teaches the pRSET A, B, C vectors for prokaryotic expression of proteins (page 37), host cells comprising the vectors and pRSET A. B, C vectors comprising a recombinant protein as a positive expression control (page 37, Contents and Storage). These vectors all comprise the nucleotide sequence encoding the enterokinase cleavage site (page 37, Description) which contains the peptide Asp-Asp-Asp-Asp-Lys (DDDDK). See page 12, right column, Description. pRSET A, B, C also contain a polynucleotide sequence encoding a polyhistidine tag (His6). The cloning site in pRSET A, B, C (i.e. MCS) is immediately after the polynucleotide encoding the enterokinase cleavage site, and the polynucleotide encoding the enterokinase cleavage site is immediately after the polynucleotide encoding His6. pRSET A, B, C do not have a polynucleotide encoding an IgG (k) or a trypsin signal peptide. A target protein produced using the pRSET vectors would be a recombinant fusion protein until enterokinase is used to cleave the His6 tag. In addition, the Invitrogen 1997 catalog teaches the pSecTag2 vectors for expression in mammalian cells. psecTag2 vectors comprise a polynucleotide encoding the mouse IgG(k) secretion signal, a cloning site, a polynucleotide encoding the C-terminal c-myc epitope for detection with the anti-myc antibody, and a polynucleotide encoding a His6 tag (page 46, left column, Description).

9. Applicants argue that while it is agreed that the 1997 Invitrogen Catalog teaches a vector capable of expressing proteins by combining a secretion signal peptide, a tag, a cleavage site and a cloning site, the vector of the present invention contains these elements in a particular order, i.e. a secretion signal, a tag, a cleavage site, and a cloning site. Applicants argue that a protein

produced expressed using the vector of the invention results in a protein comprising a secretion signal, a tag, and a cleavage site at the N-terminus of the protein of interest. It is Applicant's contention that while the components of the vector of the present invention were known, the new advantageous effects of an expressed protein containing these elements in the order specified, i.e. secretion signal which allows secretion outside the host cell, a tag which allows easy purification, and a cleavage site which allows enzymatic removal of the tag and cleavage site from the protein of interest with no extra amino acids added at the C-terminus is neither disclosed nor suggested by the cited reference.

10. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. While the Examiner agrees that the reference does not teach one single vector which comprises all the elements required in the order recited in the claim, the Examiner disagrees with Applicant's contention that the reference does not teach or suggest a vector comprising the elements in the order recited. Vector pRSET comprises all the elements required in the vector of claim 1 in the order recited with the exception of the secretion signal, i.e. His6 tag, enterokinase cleavage site, and multiple cloning site in that order. See page 37 of the 1997 Invitrogen Catalog, diagram on the right. The only element missing in the pRSET vector is the secretion signal. Vector pSecTag teaches the secretion signal, multiple cloning site, myc epitope, and His6 tag, in that order. Since it is well known in the art that the secretion signal must be placed before the desired protein/fusion protein for secretion to occur, if one were to use a secretion signal, the secretion signal would have to be placed first. See, for example, Glick et al., Molecular Biotechnology: Principles and Applications of Recombinant DNA, 1994, pages 106-107; 118-119, where it is stated that a polynucleotide encoding a signal peptide is always placed just upstream of the cDNA encoding the protein of interest (i.e. N-terminus). Furthermore, contrary to Applicant's assertion, vector pRSET clearly teaches a vector which would express a protein having the His6 tag and enterokinase cleavage site at the N-terminus, as evidenced by the

fact that the elements in pRSET are in the same order as those recited in the claims, therefore resulting in the desired protein free of any additional amino acids at the C-terminus. It is also noted that the limitation in claim 12 regarding an epitope is clearly taught by vector pSecTag as it contains a myc epitope next to the His6 tag. Since claim 12 is directed to the vector of claim 1 with the added limitation of further comprising a polynucleotide encoding an antibody recognition epitope in any location (i.e. no limitation regarding the location of this polynucleotide is recited), the 1997 Invitrogen Catalog clearly renders the claimed invention obvious to one of skill in the art for the reasons of record.

11. As indicated previously , a person of ordinary skill in the art is motivated to modify the pRSET vector such that the IgG(k) secretion signal and the c-myc epitope of the pSecTag vector are added for the benefit of creating an expression vector which allows for secretion of the desired protein and an additional purification tag. Similarly, a person of ordinary skill in the art is motivated to modify the pSecTag vector by adding the pRSET's polynucleotide encoding the enterokinase cleavage site to the pSecTag vector next to the His6 tag for the benefit of being able to cleave the His6 tag from the target protein after purification. A person of ordinary skill in the art is motivated to place the polynucleotide encoding the His6 tag prior to the cloning site since the His6 tag may affect folding/activity of the fusion protein if placed at the C-terminus. In addition, it is noted that the location of the His6 tag , i.e. C-terminus or N-terminus with respect to the protein of interest, while it may affect the folding/activity of the fusion protein containing the protein of interest before enterokinase is used, it should not be an issue once it is removed by enterokinase. Also, a person of ordinary skill in the art is motivated to transform host cells with said vectors to produce a recombinant fusion protein comprising the target protein which is easier to purify as it would be secreted to the medium and could be further purified/identified with an anti-myc antibody. The benefits of secreting a recombinant protein are well known in the art as secretion to the extracellular medium avoids additional steps in the isolation and purification of

the desired protein. See, for example, Glick et al., Molecular Biotechnology: Principles and Applications of Recombinant DNA, 1994, page 106, Increasing Secretion, last sentence, where it is stated that proteins which are secreted are easier to purify. The benefits of adding an additional purification/identification tag are well known in the art as additional tags would allow for additional flexibility in the purification process and possibly additional purity.

12. One of ordinary skill in the art has a reasonable expectation of success at modifying the pRSET vector to include a polynucleotide encoding the IgG(k) secretion signal of the pSecTag vector or modify the pSecTag vector such that the His6 tag is placed on the N-terminus of the desired protein and to an enterokinase cleavage site next to the His6 tag, since the Invitrogen 1997 catalog teaches expression vectors comprising all the required elements, i.e. IgG(k) secretion signal, His6 tag, enterokinase cleavage site, myc epitope, and cloning site. Furthermore, the molecular biology techniques required to place the required elements in the order recited are well known in the art. One of skill in the art has a reasonable expectation of success at transforming a host cell with the vectors of the Invitrogen 1997 catalog and producing recombinant fusion proteins such as proteins comprising histidine tags, since transformation of host cells with vectors and production of recombinant proteins with such host cells is well known and widely used in the art. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

13. The rejections previously applied are, therefore, maintained for the reasons of record and those set forth above in view of the non-entry of the proposed amendments.

14. Claims 5-6, 13, 17 appear to be allowable over the prior art of record but are rejected as they depend upon a rejected base claim.

15. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to: NONE

Claim(s) rejected: 1-6, 12-18, 20, 25, 27, 30

Claim(s) withdrawn from consideration: 19, 21-24, 26, 28-29

16. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

17. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
August 16, 2004

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